

CLAIMS:

1. (Original) A therapeutic bioconjugate comprising:
 - a. a hydrophilic polymer; and
 - b. one or more peptides capable of binding specifically to a ligand expressed on a cell surface.
2. (Original) The bioconjugate of Claim 1 for blocking interactions between cells in a living tissue wherein said ligand is expressed on the surface of at least one of said cells.
3. (Original) The bioconjugate of Claim 1 for blocking interaction between a cell and an extracellular matrix wherein said ligand is capable of binding to a component of said matrix.
4. (Original) The bioconjugate of Claim 1 for blocking pathological reactions triggered by cellular interactions in a living tissue.
5. (Original) The bioconjugate of Claim 1 wherein said peptide comprises the amino acid sequence of the binding portion of an integrin for said ligand.
6. (Original) The bioconjugate of Claim 5 for blocking cell signaling receptors implicated in the regulation of cellular adhesion, migration, tumor metastasis, proliferation, angiogenesis, bone resorption, apoptosis, or gene expression.
7. (Original) The bioconjugate of Claim 5 wherein said binding portion is from an integrin α subunit or an integrin β subunit.
8. (Original) The bioconjugate of Claim 7 comprising one or more peptides selected from the group consisting of SEQ ID NOS 1-202.

9. (Original) The bioconjugate of Claim 7 wherein said binding portion is a portion of the integrin α_2 subunit (CD49b, VLA-2, platelet gpla) I domain, integrin α_4 (CD49b, VLA-4), integrin α_5 (CD49e, VLA-5), integrin α_L (CD11a) I domain, integrin α_M subunit (CD11b) I domain, integrin α_{IIb} I domain, integrin α_{IIb} (CD41) heavy chain, integrin α_{IIb} (CD41) light chain, integrin β_1 (CD29) subunit, the integrin β_2 (CD18) subunit, integrin β_3 (CD61) subunit, or integrin β_7 (LPAM-1) subunit.

10. (Original) The bioconjugate of Claim 9 wherein said peptide comprises the binding portion of the integrin α_2 subunit (CD49b, VLA-2, platelet gpla) I domain and binds specifically to ligands CN I, CN II, CN III, CN IV, LN or the echovirus-1 receptor.

11. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_4 (CD49b, VLA-4) subunit that binds specifically to the ligands VCAM-1, FN, MAdCAM-1, TSP or invasin.

12. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_5 (CD49e, VLA-5) that binds specifically to ligands FN, L1 or invasin.

13. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_1 (CD11a) I domain that binds specifically to the ligands ICAM-1, ICAM-2, ICAM-3 or LPS.

14. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_M subunit (CD11b) I domain that binds specifically to the ligands iC3b, ICAM-1, ICAM-2, ICAM-4, Fb, Factor X, CD23, NIF, heparin, beta glucan, or LPS.

15. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_{IIb} (CD41) heavy chain that binds specifically to the ligands Fb, FN, VN, TSP or vWF.

16. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin α_{11b} (CD41) light chain that binds specifically to the ligands Fb, FN, VN, TSP and vWF.

17. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin β_1 (CD29) subunit, and binds specifically to the ligands FN,LN,CN,VCAM-1, FN, MAdCAM-1, TSP or invasin.

18. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin β_2 (CD18) subunit that binds specifically to the ligands ICAM-1, ICAM-2, ICAM-3, ICAM-4, LPS, iC3b, Fb, Factor X, CD23, NIF, heparin, or betaglucan.

19. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin β_3 (CD61) subunit that binds specifically to ligands fibrinogen, fibronectin, vitronectin, thrombospondin, von Willebrand factor, osteopontin, bone sialoprotein, laminins, collagens, or neural cell adhesion molecule L1.

20. (Original) The bioconjugate of Claim 9 wherein said peptide comprises a portion of the integrin β_7 (LPAM-1) subunit that binds specifically to the ligands VCAM-1, fibronectin, MAdCAM-1, or E-cadherin (cadherin-1).

21. (Withdrawn) The nucleic acids having the sequence coding for peptides of the bioconjugate of Claim 8.

22. (Withdrawn) The nucleic acids of Claim 21 selected from the group consisting of SEQ ID NOS 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 86, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137,

139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 186, 185, 187, 189, 191, 193, 195, 1197, 199 and 201.

23. (Withdrawn) The peptide for preparation of the bioconjugate of Claim 1, said peptide having a sequence selected from the group consisting of SEQ ID NOS 1-112, wherein each sequence comprises additionally an N-terminal and/or a C-terminal cysteine residue.

24. (Withdrawn) The nucleic acids having the sequence coding for a peptide of Claim 23.

25. (Original) The bioconjugate of Claim 1 wherein said polymer is a polysaccharide or an oligosaccharide.

26. (Original) The bioconjugate of Claim 1 wherein said polymer is a derivative of a polysaccharide or an oligosaccharide wherein said derivative polymer additionally comprises additional groups capable of reacting chemically with a peptide to form said bioconjugate.

27. (Original) The bioconjugate of Claim 1 having the formula XY_b wherein X is a low cell-adhesive, hydrophilic polymer, Y is a peptide comprising a portion of the binding site of an integrin for a ligand expressed on a cell surface, and b is greater than 0.

28. (Original) The bioconjugate of Claim 27 wherein X comprises a polysaccharide or an oligosaccharide.

29. (Original) The bioconjugate of Claim 27 wherein X comprises a derivative of a polysaccharide or of an oligosaccharide wherein said derivative saccharide comprises reactive groups whereby said derivative saccharide reacts with said peptide to form said bioconjugate.

30. (Original) The bioconjugate of Claim 29 wherein said reactive group comprises a hydroxyl group.

31. (Original) The bioconjugate of Claim 25 wherein said polysaccharide or oligosaccharide is selected from the group consisting of agarose, dextran, heparin, chondroitin sulfate, hydroxyethyl starch, and hyaluronic acid.

32. (Original) The bioconjugate of Claim 1 wherein said polymer comprises a dextran and said peptide comprises the binding portion of an integrin for its ligand.

33. (Original) The bioconjugate of Claim 1 wherein said polymer is polyvalent and is selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(acrylic acid), poly(ethylene-co-vinyl alcohol), poly(vinyl pyrrolidone), poly(ethyloxazoline), and poly(ethylene oxide)-co-poly(propylene oxide) block copolymers.

34. (Original) The bioconjugate of Claim 1 wherein said polymer comprises copolymers, block copolymers, graft copolymers, alternating copolymers, or random copolymers.

35. (Original) The bioconjugate of Claim 1 wherein said polymer is essentially inert.

36. (Original) The bioconjugate of Claim 1 wherein said polymer is degradable by hydrolytic or enzymatic means.

37. (Original) The bioconjugate of Claim 36 wherein said degradable polymer comprises one or more blocks selected from the group consisting of lactic acid, glycolic acid, ϵ -caprolactone, lactic-co-glycolic acid oligomers, trimethylene carbonate, anhydrides, and amino acids.

38. (Original) The bioconjugate of Claim 1 wherein said polymer is a serum protein.

39. (Original) The bioconjugate of Claim 38 wherein said serum protein is an albumin.

40. (Original) The bioconjugate of Claim 1 in a pharmaceutically acceptable carrier.

41. (Original) The bioconjugate of Claim 1 immobilized on a solid substrate.

42. (Original) The bioconjugate of Claim 41 wherein said substrate is an implantable medical device.

43. (Original) The bioconjugate of Claim 42 wherein said medical device is a drug delivery device.

44. (Original) The bioconjugate of Claim 41 wherein said substrate is a component of an *in vitro* diagnostic device.

45. (Original) The kit comprising one or more bioconjugates of Claim 1 and reagents and apparatus suitable for administering said bioconjugate to an individual.

46. (Original) The kit of Claim 45 wherein said bioconjugate is in a pharmaceutically acceptable carrier.

47. (Withdrawn) The biointerface formed on a mammalian tissue, wherein said biointerface comprises a plurality of bioconjugates of Claim 1 bound to a plurality of ligands on said tissue.

48. (Withdrawn) A method of preparing a bioconjugate comprising the steps of:

a. providing a hydrophilic polymer having one or more reactive groups;

b. providing a bioselective peptide comprising a chemical group capable of reacting with said reactive groups; and

c. contacting said polymer and said peptide under conditions whereby said reactive and chemical groups react to form said bioconjugate.

49. (Withdrawn) The method of Claim 48 wherein the reactive groups of said polymer are hydroxyl groups and the chemical group of said peptide is a sulphydryl group.

50. (Withdrawn) The method of Claim 48 wherein said polymer is a polysaccharide.

51. (Withdrawn) The method of Claim 50 wherein said polysaccharide is activated dextran.

52. (Withdrawn) The method of Claim 50 wherein said polysaccharide is hydroxyl starch.

53. (Withdrawn) The method of Claim 50 wherein said peptide is selected from the group consisting of SEQ ID NOS 7-14, 25-32, 35-38, 43-48, 55-56, 65, 66, 93, 94, 97, 98, 107-110, 119-124, 133-136, 141, 142, 153, 154, 157-164, 171-174, 179-200, 203-212, 215 and 216, said peptide comprising a cysteine residue.

54. (Withdrawn) The method of Claim 50 wherein said peptide is selected from the group consisting of SEQ ID NOS 1-218, said peptide comprising in addition an N-terminal or a C-terminal cysteine residue.

55. (Withdrawn) A method of preparing a bioconjugate comprising the steps of:

- a. providing a peptide selected from the group consisting of SEQ ID NOS 1-218;
- b. modifying said peptide by addition of an N-terminal or C-terminal cysteine residue;
- c. providing an amount of activated dextran; and
- d. contacting said activated dextran and said modified peptide under conditions, whereby said dextran and said modified peptide react to form said bioconjugate.

56. (Withdrawn) A method for preventing adhesion of a mobile cell to a cell immobilized on a substrate comprising the step of applying a bioconjugate specific for said immobilized cell under such conditions that said bioconjugate forms a cell adhesion barrier on said immobilized cell.

57. (Withdrawn) A method of blocking pathological reactions triggered by cellular interactions in a living tissue, said method comprising the step of administering to the living tissue a bioconjugate selective for a target tissue whereby the bioconjugate forms a cell adhesion barrier at a targeted tissue site.

58. (Withdrawn) The method of Claim 57, wherein said bioconjugate comprises the binding portion of an integrin for a ligand expressed in said target tissue.

59. (Withdrawn) The method of Claim 58 wherein said bioconjugate is administered intravascularly, orally, intramuscularly, intraperitoneally, subcutaneously, cerebrospinally, endovascularly, rectally or topically.

60. (Withdrawn) The method of Claim 59 wherein said bioconjugate is administered intravascularly in a biologically compatible solution at a concentration of between about 1 µg/L and 100 g/L.

61. (Withdrawn) The method of Claim 58 wherein said bioconjugate is administered to an individual in a pharmaceutically acceptable composition.

62. (Withdrawn) The method of Claim 58 wherein the amount of administered bioconjugate is between about 1-1000 mg/kg body weight.

63. (Withdrawn) The method of Claim 57 for preventing and treating thrombosis, wherein an anti-coagulating amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on inflamed endovascular cells is administered to tissue containing said inflamed endovascular cells.

64. (Withdrawn) The method of Claim 63 wherein said integrin ligands are CN I-IV, LN, or the Echovirus-1 receptor.

65. (Withdrawn) The method of Claim 63 wherein said peptide is selected from the group consisting of P-2, P-49, and SEQ ID NOS 1, 2, 3-8, 91-106, 129-192, 203 and 204.

66. (Withdrawn) The method of Claim 57 for preventing and treating atherosclerosis, wherein an anti-atherosclerotic effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on or around atherosclerotic cells is administered to tissue containing said atherosclerotic cells.

67. (Withdrawn) The method of Claim 66 wherein said integrin ligands are VCAM-1, FN, MAdCAM-1, TSP, invasin or a combination thereof.

68. (Withdrawn) The method of Claim 66 wherein said peptide is selected from the group consisting of P-49 and SEQ ID NOS 9-38, 59-106, 129-202 and 207-210.

69. (Withdrawn) The method of Claim 57 for preventing and treating systemic inflammatory response syndrome wherein an effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on cells in inflamed tissue is administered to said tissue.

70. (Withdrawn) The method of Claim 69 wherein said integrin ligands are FN, L1 or invasin.

71. (Withdrawn) The method of Claim 69 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 9-38, 59-106, 129-202 and 207-210.

72. (Withdrawn) The method of Claim 58 for preventing and treating multiple organ failure wherein an failure effective amount of said bioconjugate comprising one or more peptides

capable of binding selectively to integrin ligands expressed on cells in affected tissue is administered to said tissue.

73. (Withdrawn) The method of Claim 72 wherein said integrin ligands are ICAM-1, ICAM-2, ICAM-3, LPS or a combination thereof.

74. (Withdrawn) The method of Claim 72 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 39-58, 107-128 and 211-218.

75. (Withdrawn) The method of Claim 57 for preventing and treating autoimmune disease wherein an effective amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on cells implicated in the autoimmune disease is administered to tissue containing said cells.

76. (Withdrawn) The method of Claim 75 wherein said integrin ligand is VCAM-1, FN, MAdCAM-1, TSP, invasin, ICAM-1, ICAM-2, ICAM-3, LPS, iC3b, ICAM-1, ICAM-2, ICAM-4, Fb, Factor X, CD23, NIF, heparin, β -glucan, LPS, FN, Fb, CN I, VN, FN, LN, CN, Fb, Factor X, CD23, NIF, heparin, β -glucan or a combination thereof.

77. (Withdrawn) The method of Claim 75 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-2, P-49 and SEQ ID NOS 1-218.

78. (Withdrawn) The method of Claim 57 for preventing and treating inflammatory diseases wherein an effective amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on cells of inflamed tissue is administered to a tissue containing said inflamed cells.

79. (Withdrawn) The method of Claim 78 wherein said integrin ligand is CN I-IV, LN, Echovirus-1 receptor, VCAM-1, FN, MAdCAM-1, TSP, Invasin, L1, LPS, ICAM-1-4, iC3b, Fb, Factor X, CD23, NIF, heparin, β -glucan, VN, vWF or a combination thereof.

80. (Withdrawn) The method of Claim 78 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-2, P-49, and SEQ ID NOS 1-202 and 205-219.

81. (Withdrawn) The method of Claim 58 for preventing and treating allograft transplant rejection wherein an anti-rejection amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on T cells implicated in allograft transplant rejection is administered to an individual having transplanted tissue.

82. (Withdrawn) The method of Claim 81 wherein said integrin ligand is VCAM-1, FN, MAdCAM-1, TSP, invasin, ICAM-1-4, LPS, iC3b, Fb, Factor X, CD23, NIF, heparin, β -glucan, LN, CN, vWF, OP, BSP, L1 and E-cadherin.

83. (Withdrawn) The method of Claim 81 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 9-30, 39-58, 91-200 and 211-218.

84. (Withdrawn) The method of Claim 81 further comprising concurrent administration of an immunosuppressant.

85. (Withdrawn) The method of Claim 84 wherein said immunosuppressant is cyclosporine.

86. (Withdrawn) The method of Claim 58 for preventing and treating Crohn's disease wherein an effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on inflamed cells in gut tissue is administered to said gut tissue.

87. (Withdrawn) The method of Claim 86 wherein said integrin ligand is VCAM-1, FN, MAdCAM-1, TSP, invasin, ICAM-1-4, iC3b, Fb, Factor X, CD23, NIF, heparin, β -glucan, CN I, VN, LN, OP, BSP, L1, vWF and E-cadherin.

88. (Withdrawn) The method of Claim 86 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 9-30, 30-58, 93-200 and 211-218.

89. (Withdrawn) The method of Claim 58 for preventing and treating inflammatory bowel disease wherein an effective amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on inflamed cells in gut tissue is administered to said gut tissue.

90. (Withdrawn) The method of Claim 89 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 9-30, 39-58, 91-200 and 21-218.

91. (Withdrawn) The method of Claim 58 for preventing and treating sequelae of a bacterial infection wherein an effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands expressed on secretory membranes is administered to said secretory membranes.

92. (Withdrawn) The method of Claim 91 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 39-58, 107-192 and 211-216.

93. (Withdrawn) The method of Claim 58 for preventing and treating sepsis or septic shock, comprising administering an effective amount of a bioconjugate comprising one or more

peptides capable of binding selectively to integrin ligands such as LFA-1, ICAM-1, VCAM-1 and a combination thereof.

94. (Withdrawn) The method of Claim 93 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P2, P-49 and SEQ ID NOS 1-30, 39-58, 91-200 and 211-18.

95. (Withdrawn) The method of Claim 57 for preventing and treating ischemia-reperfusion injury, comprising administering an effective amount of a bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands intravenously.

96. (Withdrawn) The method of Claim 95 wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 9-30 and 39-218.

97. (Withdrawn) The method of Claim 57 for preventing and treating cancer metastasis, comprising administering wherein an anti-metastasis effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to integrin ligands systemically to an individual or locally to tissue containing or suspected of containing said cancer.

98. (Withdrawn) The method of Claim 97, wherein said bioconjugate comprises one or more peptides selected from the group consisting of P-49 and SEQ ID NOS 91, 92, 203 and 204.

99. (Withdrawn) The method of Claim 57 for treating conditions caused by viper and rattlesnake bites wherein an anti-venom effective amount of said bioconjugate comprising one or more peptides capable of binding selectively to at least one integrin ligand on a bitten tissue site is administered.

100. (Withdrawn) The method of Claim 110 wherein said bioconjugate comprises a peptide having SEQ ID NOS 153 and 154.

101. (Original) Therapeutic replacement fluids comprising a bioconjugate of Claim 1 and a pharmaceutically acceptable diluent.